Bohn, Brent

From: Gibbons, Catherine
Sent: Friday, December 04, 2015 7:38 PM
To: Bohn, Brent
Subject: FW: More!
Attachments: 2_Proctor Q2.pptx; 2_Suh_Cr Issue2_Suh.pptx; 1_Proctor Q1.pptx; 1_Suh_Cr Issue 1 _Suh.pptx; 4_Proctor Q4.pptx; 5_Proctor Q5.pptx; 7_Proctor Q7.pptx

From: Gibbons, Catherine
Sent: Tuesday, October 28, 2014 7:13 PM
To: Elaine.Khan@oehha.ca.gov
Subject: More!

Science Question 2: Lung Cancer Dose-Response Modeling of the Painesville Cohort

Key Points

1. **A mortality follow-up and lung cancer risk assessment study [Funded by EPRI] is nearing completion and should be considered by EPA for quantitative dose-response modeling of inhalation cancer risk.**
2. **Relative risk and additive risk models of Poisson regressions show good fits to lung cancer mortality data based on the cumulative exposure metric.**
3. **For all models, an effect of Cr(VI) exposure appears to begins ~1 mg/m^3-year (equivalent to a 40-year occupational exposure to 25 µg/m^3).**

Deborah Proctor

ToxStrategies, Inc.

October 29, 2014

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Lung Cancer Dose-Response Modeling: Poisson Regressions

- **Painesville lung cancer mortality data were categorized by age (10 categories, < 45, 45-49, 50-54, … > 85) and cumulative exposure (10 categories chosen with equal number of lung cancers)**
- **As defined in Crump et al. (2003), relative risk and additive risk models were tested using various lagged exposures and Poisson regression**
- **Cox regression analyses are on-going**
- **All analyses were conducted using SAS**

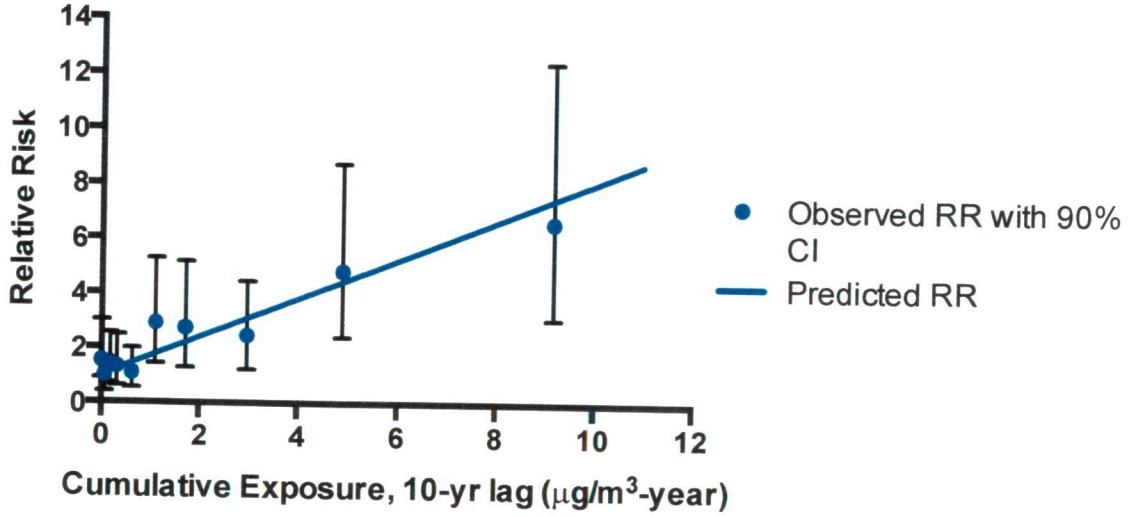
Preliminary Results: Potency Factors for Cr(VI) based on Cumulative Exposure, Various Lags

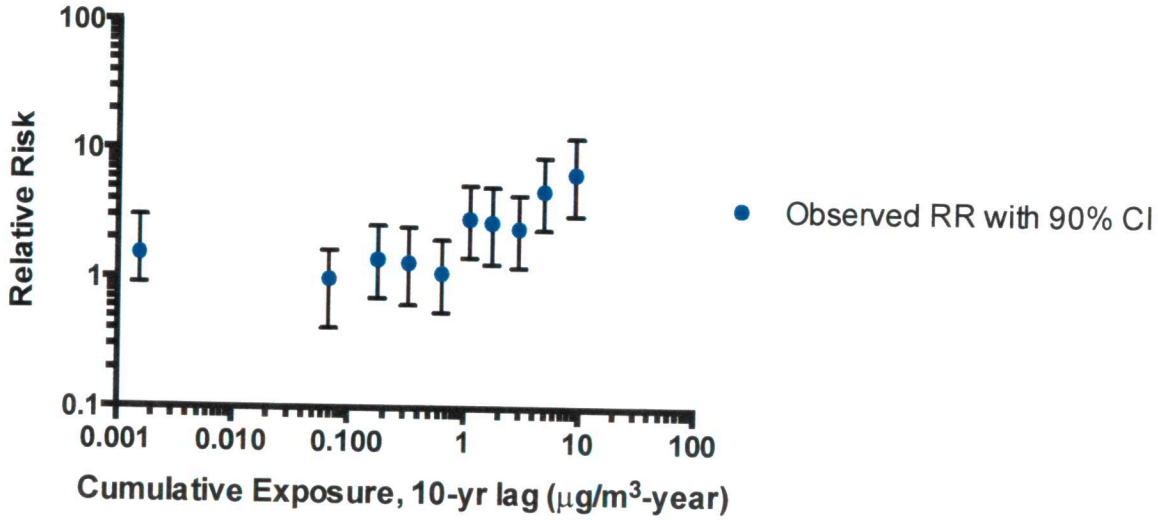
Model	β Estimate (Potency Factor)
Relative Risk Model	
No lag	0.725
5-year lag	0.732
10-year lag	0.703
15-year lag	0.670
Additive Risk Model	
No lag	0.00118
5-year lag	0.00127
10-year lag	0.00135
15-year lag	0.00169
Crump et al. (2003)	
5-year lag, α=1	
Relative risk	0.794 (90% CI
Additive risk	0.00161 (90% CI

$\beta = (mg/m^3\text{-year})^{-1}$ for the relative risk model

$\beta = (mg/m^3\text{-year per person-year})^{-1}$ for the additive risk model

Preliminary Results: Fit of Relative Risk Model Cumulative Exposure, 10-year lag





Graphical representation in log space for resolution in the low dose range

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Preliminary Conclusions for Lung Cancer Dose-Response Modeling

- **For all relative risk and additive risk models, statistical evidence for an effect of Cr(VI) exposure begins at about 1 mg/m^3-year (equivalent to a 40-year occupational exposure to 25 µg/m^3)**
- **Preliminary modeling results appear to be roughly comparable with the results in Crump et al. (2003)**

Meta-Analysis Considerations

- **Steps for conducting meta-analysis (based on Crump and Allen et al. 2010, "*Towards Making Epidemiologic Data More Useful for Quantitative Risk Assessment*")**
  - Use unprocessed data of the Baltimore cohort for both lung cancer and cumulative exposure metric
  - Combine with unprocessed Painesville cohort data
  - Use Poisson regression and Cox regression models
  - Use life table analyses to estimate IURs
- **Potential future study**

Meta-Analysis Considerations: Example Haney et al. 2014; TCEQ 2014

- ✓**Used data from the Painesville (published) and Baltimore (un-publishd) cohorts**
- ✓**Conducted Cox regression models of the Baltimore cohort data**
- ✓**Included life table analysis for the current US population**

Source	Study	URF ($\mu g/m^3)^{-1}$ (MLE)
Haney/TCEQ 2014	Painesville (Luippold 2003)	2.1E-3
	Baltimore (Gibb 2000)	2.8E-3
	Combined Studies	**2.4E-3**
Compared to that from supporting study Applied Epi (2002)		4.3E-3

Science Question 1: Methodological Considerations for Evaluating Epidemiologic Studies

Key Points

1. **There are many methodological characteristics for Cr(VI) occupational cohort studies of lung cancer to be considered relative to their use in risk assessment.**
2. **Overall, the effects of potentially biasing characteristics of the primary studies will result in an overestimate of lung cancer risk at low environmentally-relevant exposures**

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Comparison of occupational and environmental ambient Cr(VI) exposure concentrations

Baltimore and Painesville cohort studies:

- Painesville 1940-1972
- Average exposures ranged from 39 to 720 $\mu g/m^3$ (Proctor et al. 2003)
- Baltimore 1950-1986
- Average exposures ranged from 31 to 213 $\mu g/m^3$ (Braver et al. 1985; Gibb et al. 2000)

Ambient monitoring data

- NJ 1990s: 1.2 ng/m^3 (Falerios et al. 1992)
- Ontario 1996: 0.55 ng/m^3 (Bell and Hipfner 1997)
- Southern California 2008:
  - Mean 0.2 ng/m^3
  - Upper bound Near cement plants: 5 ng/m^3

  (SCAQMD 2008)

Difference in airborne concentration is in the range of 10^5-10^6 between historical chromate production industries and current environmental exposures

Lung Cancer Risk Assessment for Cr(VI): Judging Validity and Bias

"A study is externally valid if the study results for the study population can be extrapolated to external target populations. An internally valid study is free from different types of biases, and is a prerequisite for generalizing study results beyond the study population"
EPA 2014, Preliminary Materials page 1-10/11

- **No exposure-response study of Cr(VI)-exposed populations exist that is "free from different types of bias" and is externally valid, without limitations, for environmentally-exposed populations in the US.**
- **Nonetheless, it is expected that data from workers studies will be used to develop a cancer risk assessment.**
- **How will EPA judge/address internal and external validity for these studies and others is the critical question.**

Chromate Production Industry Studies: Factors that May Bias Risk Estimates

Dose-rate effect

- Both animal (Steinhoff et al. 1986) and human (Gibb et al. 2011) studies indicate that a dose-rate effect exists for lung cancer

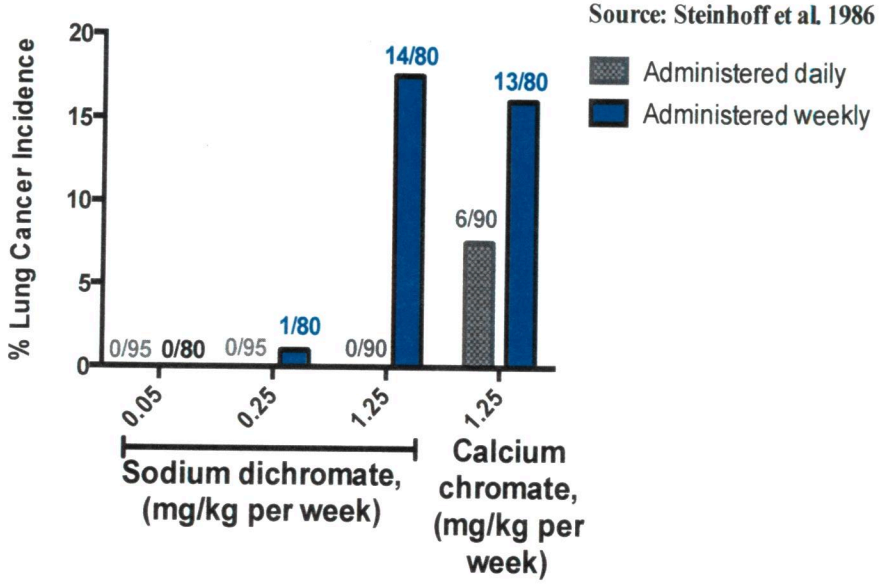

Table 4. **Relative risks (95% Confidence Intervals) of Lung Cancer Mortality for Exposure to 0.339 mg/m^3-Years of Cumulative Hexavalent Chromium (the Median of the 4th Quartile of Exposure) for Smokers and Nonsmokers for Different Work Durations Adjusted by Age at Hire, Work Duration, and Associated Cr6 Interaction Terms**

	30 Days	6 Months	1 Year	5 Years	10 Years
Smokers	1.41 (1.07 – 1.85)	1.40 (1.05 – 1.85)	1.39 (1.03 – 1.86)	1.32 (0.87 – 2.27)	1.24 (0.68 – 2.27)
Non-Smokers	1.82 (1.21 – 2.74)	1.81 (1.21 – 2.72)	1.80 (1.20 – 2.71)	1.71 (1.06 – 2.75)	1.61 (0.87 – 2.98)

Chromate Production Industry Studies: Factors that May Bias Risk Estimates

Workers had high rates of clinical respiratory effects in both Baltimore and Painesville cohorts

- If the MOA involves high dose effects, lung cancer risk in workers from these industries may be not be generalizable with a reasonable degree of confidence to environmentally-exposed populations
- Not all industries with Cr(VI) exposure have increased lung cancer rates associated with Cr(VI) exposure (e.g., aerospace and welding)
    - These industries also did not have significant respiratory irritation
- Draws into question the use of linear low dose extrapolation and cumulative exposure metric

Chromate Production Industry Studies: Factors that May Bias Effect and Risk Estimates

- **Asbestos and Mesothelioma**
  - Mesothelioma classification was added for ICD 10
  - In ICD 8A and 9, coding for mesothelioma is ambiguous and mesothelioma could be coded for lung cancer
  - 6 mesothelioma cases in Painesville cohort, 3 coded ICD 8A&9 as lung cancer, and 3 as mesothelioma under ICD 10
  - All of Baltimore cohort coded by ICD8A
  - As a result, some mesothelioma cases could be coded as lung cancer
- **Chemical forms**
  - Chromate production workers were exposed to sparingly soluble calcium chromates, concentrated chromic acid, soluble and insoluble salts
  - Baltimore plant also produced pigments
  - Animal data support that slightly soluble forms of Cr(VI) are of greater potency (Levy et al. 1986; Steinhoff et al. 1986)
- **Smoking/Reference Rates**
  - Preferable to use Baltimore reference rates because of higher lung cancer background rate in Baltimore
  - Smoking prevalence high in these cohorts
- **No evidence of healthy worker or survivor effect**

Chromate Production Industry Studies: Factors that May Bias Exposure and Risk Estimates

- **Exposure misclassification and error in measurement is a potential issue, especially with the older studies**
- Cr(VI) needs to be collected in a media in which it is stable to prevent reduction to Cr(III) prior to analysis
- Extraction typically conducted using water which would not extract water-insoluble fraction (~20% in roast and roast residue [PHS 1953])
- Lack of personal monitoring data, likely to result in underestimation of exposure for batch process jobs [Gibb et al. 2000])

- **For the Painesville cohort**
- Quality control evaluation supports that the data are reasonably valid (Proctor et al. 2003)
- Strong and consistent exposure-response relationship supports that exposure misclassification does not confound the exposure-response (Proctor et al. 2004)

Conclusions and Recommendation

- **Considering dose-rate effects, and based on MOA considerations, it is expected that lung cancer risk will be overestimated at low environmentally-relevant exposures by applying linear extrapolation models**
- **It is recommended that non-linear approaches be considered and compared to default linear approaches**
- Example: Haney et al. (2012, 2014), TCEQ (2014)

Approach	Chronic Reference Value (ReV)	Basis
Non-threshold	0.0043 $\mu g/m^3$	URF= 2.3×10^{-3} $(\mu g/m^3)^{-1}$
Threshold	0.24 $\mu g/m^3$	POD/UF = 7.1 $\mu g/m^3$ ÷ 30

Non-threshold ReV based on 10^{-5} risk
URF = Unit Risk Factor
POD/UF = Point of Departure/Uncertainty Factor

Science Question 4: Mechanistic Studies Database—MOA in the Lung

Key Points

- **Considerations regarding the lung cancer MOA based on recent review (Proctor et al. 2014 *Toxicology 325:*160-179)**
- **Integrated analysis of toxicokinetic, epidemiology, mechanistic and animal data**
- **Findings support a non-mutagenic MOA**

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October 30, 2014

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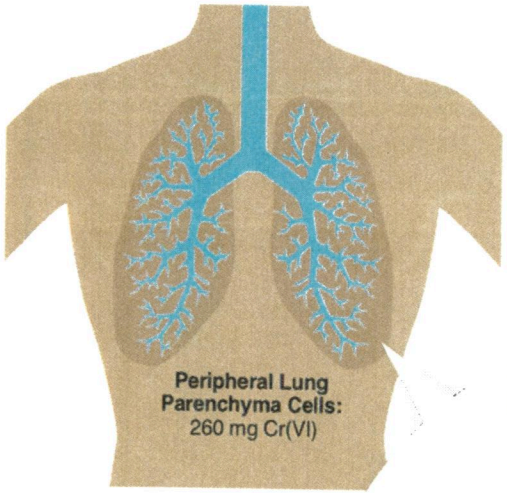
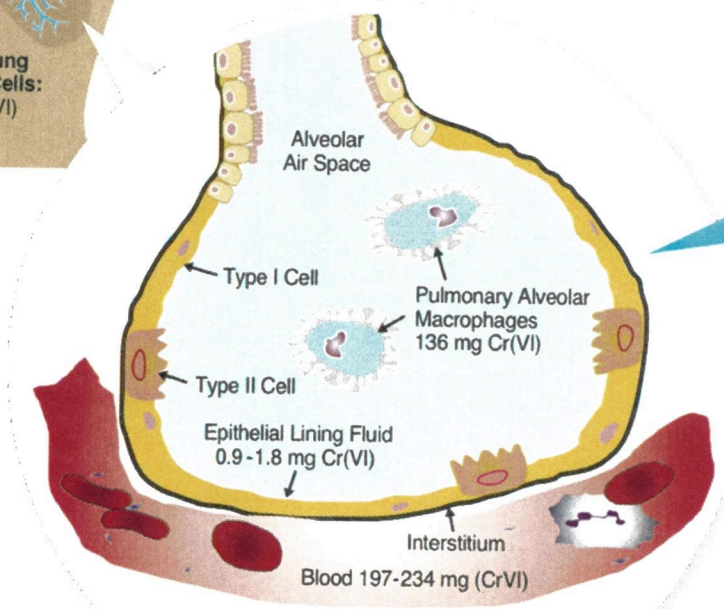
Literature Review and Analysis

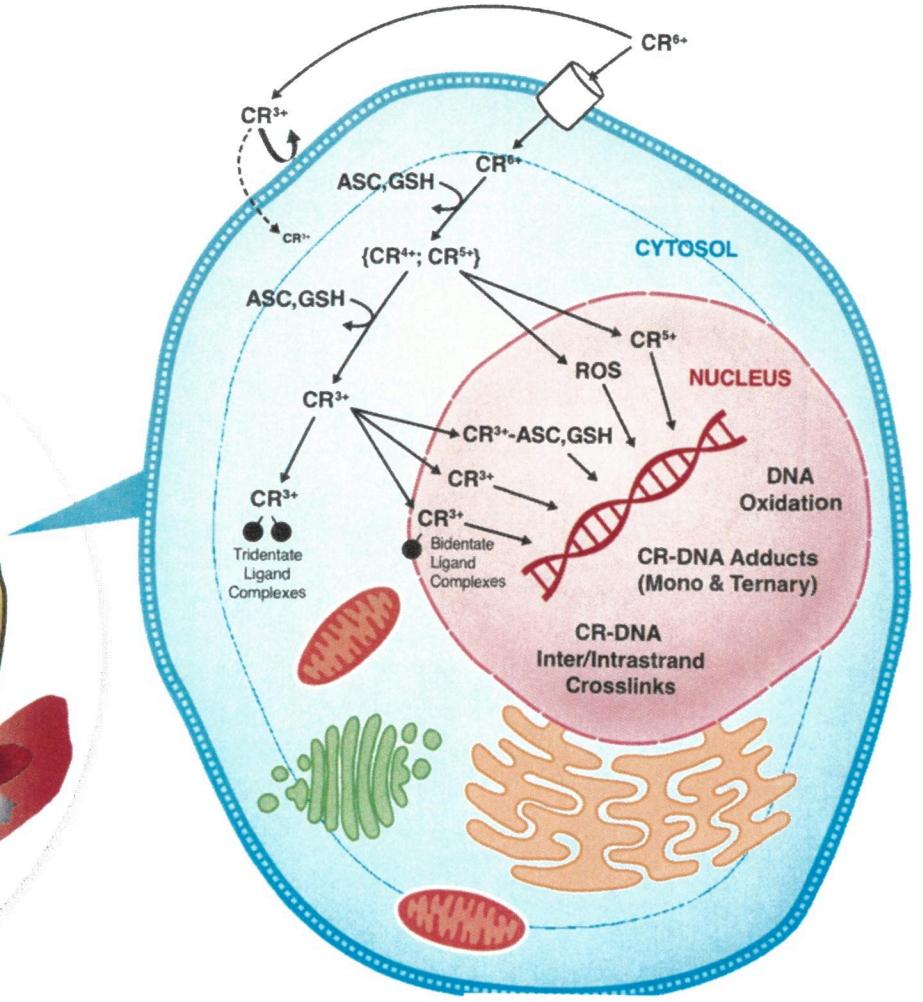
- **Kinetics Are Important**
  - *Provide biological basis for non-linearity in exposure-response (Haney et al. 2012)*
- **Focus on *in vivo* mechanistic data**
  - *Most in vivo mutagenicity data are negative*
- **Epidemiology**
  - *Strongest Cr(VI)-lung cancer associations for industries with respiratory irritation*
  - *Dose-rate effect (Gibb et al. 2011)*
  - *Some industries have no increased risk [welding (Gerin et al. 1993), aerospace (Boice et al. 1999)] but significant exposure*
- **Animal data (repeat dosing)**
  - *Role for inflammation (Beaver et al. 2009; Nickens et al. 2010)*
  - *Dose-rate effect (Steinhoff et al. 1986)*
  - *Weak carcinogen (Glaser et al. 1986)*
  - *Recovery from early tissue damage (hyperplasia and fibrosis) (Glaser et al. 1990)*

Reductive Capacity of Cr(VI) in the Lung and Published Mechanisms of DNA Damage



Based on DeFlora et al. 1997

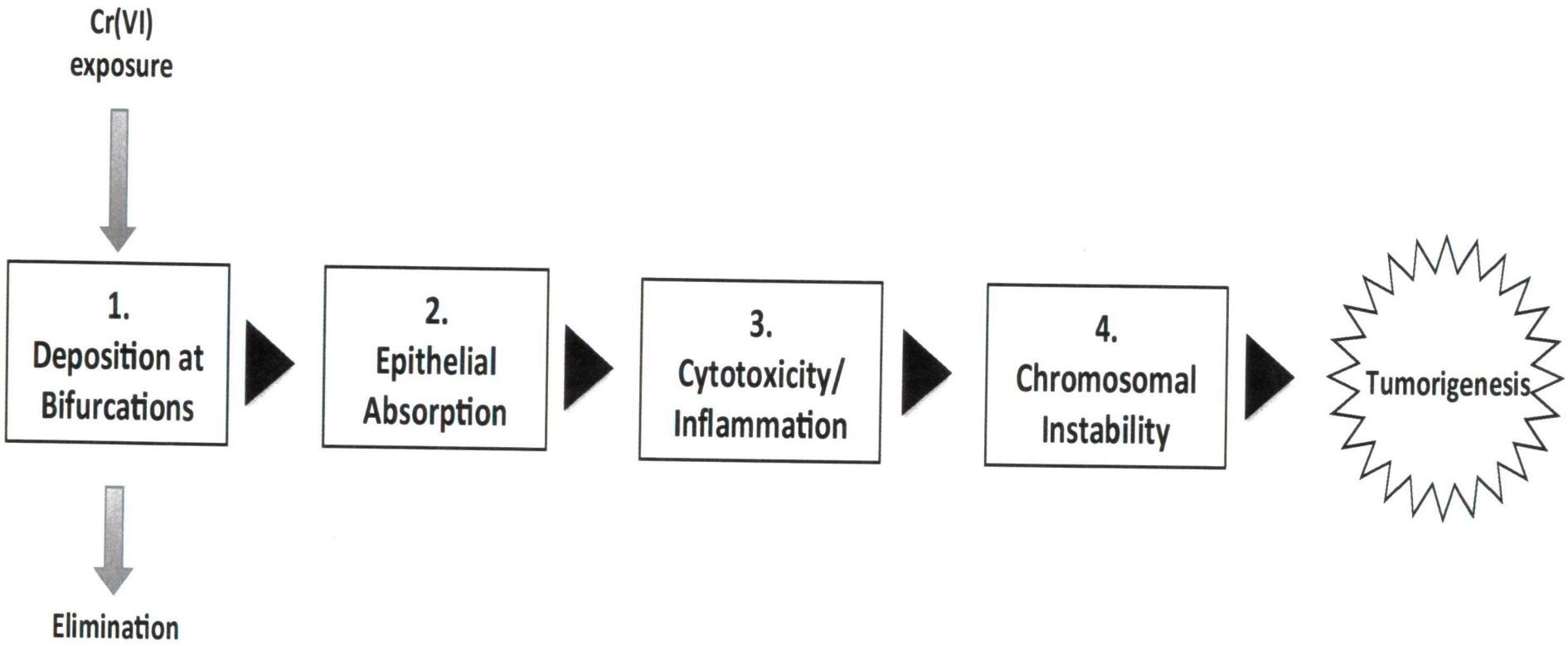




Based on O'Brien et al. 2003

Source: Proctor et al. (2014) *Toxicology*

Proposed Lung Cancer MOA



Source: Proctor et al. 2014 *Toxicology*

Comparative WOE for Non-mutagenic and Mutagenic MOA in the lung using WHO/IPCS framework

Modified Bradford Hill	Supporting Non-Mutagenic	Supporting Mutagenic MOA
Dose-response and temporal concordance	Extracellular reduction provides biological basis for non-linearity Lung tumors preceded by irritation and inflammation in both dose and time, and early hyperplasia is reversible (Glaser et al. 1986, 1990; Steinhoff et al.) Early tissue injury and inflammation in the lung in animals (Beaver et al.2009a,b) and humans (Gibb et al. 2000) In workers, lung cancer occurs after long latency period, clear evidence for cancer limited to the lung	Intratracheal instillation increased MF in Big Blue mice (Cheng et al., 2000) DNA damage after 3 days dosing at 0.25 mg/day (Izzotti et al. 1998) DNA breaks in leukocytes of mice, within 24 hrs of gavage dosing (0.18 to 24 mg/kg Cr(VI) (Danadevi et al., 2001)

Approach adapted from Meek et al. 2013)

Comparative WOE for Non-mutagenic and Mutagenic MOA in the lung using WHO/IPCS framework

Modified Bradford Hill	Supporting Non-Mutagenic	Supporting Mutagenic MOA
Consistency, specificity	Two chronic bioassays found similar non-neoplastic and neoplastic lesions in rodent lungs (Steinhoff et al., 1986; Glaser et al., 1986) Mechanistic data supports oxidative lesions, inflammation, and proliferation Clinical evidence of respiratory irritation and tissue damage in occupational cohorts with lung cancer Dose-rate effect in animals and humans (Steinhoff et al 1986; Gibb et al. 2011)	Cr(VI) is mutagenic and genotoxic in numerous *in vitro* assays, in some animal studies but by unnatural routes and at toxic doses DNA damage reported in peripheral blood lymphocytes and buccal cells among workers in two studies (Danadevi 2004; Benova 2002); however negative data are published (Gao 1994, Sarto1990) and these are not target tissues for cancer

Comparative WOE for Non-mutagenic and Mutagenic MOA in the lung using WHO/IPCS framework

Modified Bradford Hill	Supporting Non-Mutagenic	Supporting Mutagenic MOA
Biologic Plausibility	Many chromium researchers believe that Cr(VI) mutagenic potency is weak (ERD, 2011; Holmes et al. 2008). Epigenetic mechanisms identified in tumors of Cr(VI)-exposed workers (Takahashi et al. 2005); microsatellite instability (Hirose et al. 2002); low P53 mutation frequency (Kondo et al. 1997). Non-mutagenic MOA for other Cr(VI)-induced tumors (intestine and oral)	Cr(VI) is mutagenic and genotoxic in numerous *in vitro* assays, in some animal, and in humans studies

Science Question 7: *In Vivo* Mutagenicity/Genotoxicity—Oral Cavity MOA

Key Points

1. **We conducted a Big Blue transgenic rat mutation study to examine whether Cr(VI) acts by a mutagenic MOA in rat oral tissues [EPRI Funded]**
2. **Study is finished; paper has been submitted for peer-review**

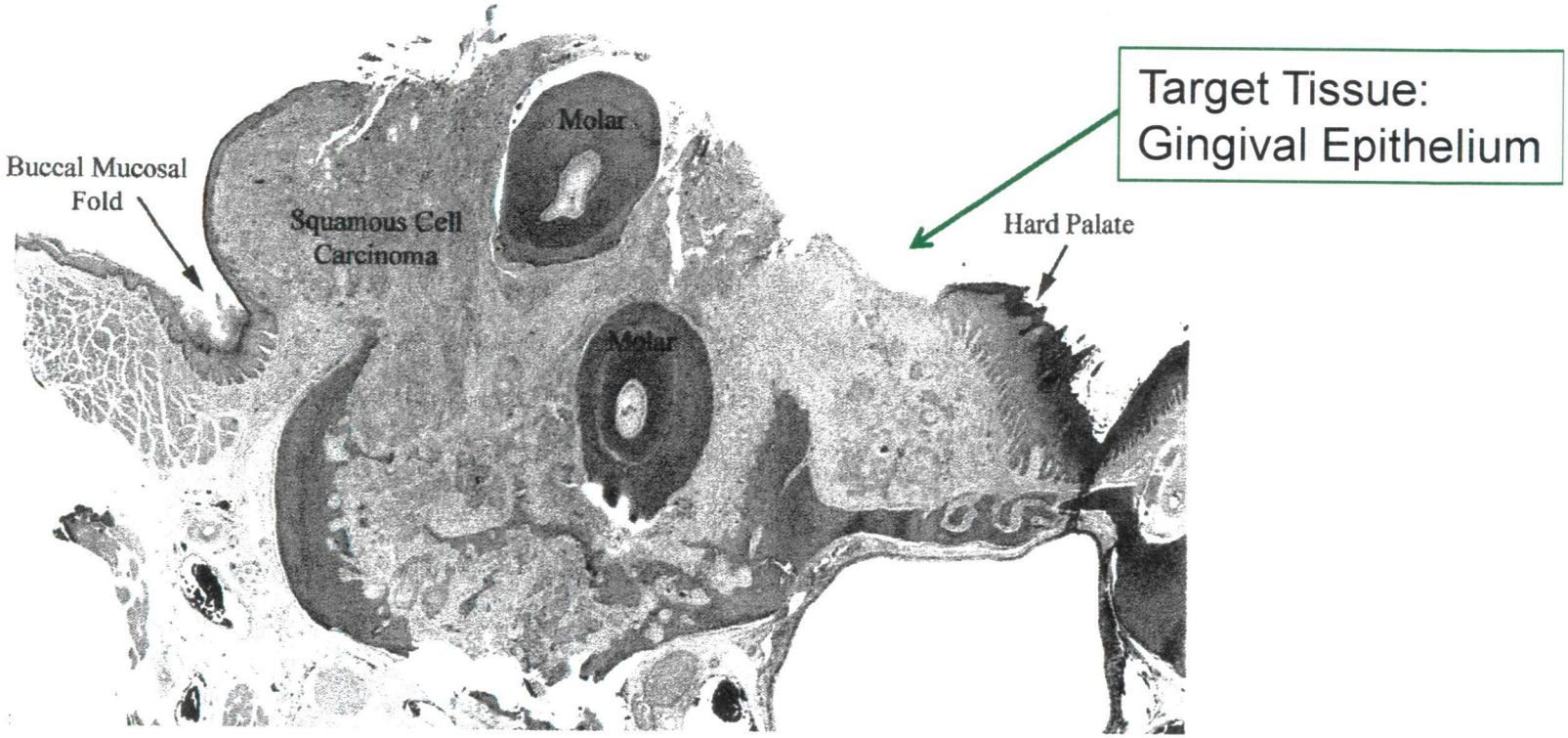
Deborah Proctor

ToxStrategies, Inc.

October 30, 2014

Transgenic Mutation Study in Big Blue Transgenic Rats

- **ToxStrategies and BioReliance conducted OECD 488, GLP-compliant transgenic mutation assays in Big Blue rats**
- **Study Objective: Examine the mutagenicity of Cr(VI) in the rat oral mucosa to inform the MOA**



Rat oral cavity squamous cell carcinoma
Source: NTP 2008

Study Design

- **Transgenic Big Blue Rats**
- **Dosing**
  - Control: Tap water
  - Positive control: 10 ppm 4-Nitroquinoline-N-oxid (4NQO) in drinking water
  - Cr(VI): 180 mgCr(VI)/L as sodium dichromate dihydrate
- **OECD 488 Dosing protocol**
  - 28 days of dosing followed by 3 days to fix mutations
  - 5 animals per exposure group

Findings & Conclusions

- **Mutation Frequency for Cr(VI) exposed rats was consistent with water controls**
- **Results argue against a mutagenic MOA in rat oral cavity**
- **Support indirect mechanisms such as those reported in Suh et al. (2014)**
  - Questions as to whether rat oral tumors are relevant – High-dose effect
  - One or multiple possible factors are observed at high dose
    - Effects on iron homeostasis (toxicogenomic analyses, Fe levels in tissues and bone marrow)
    - Decreased water intake, mild dehydration
    - Effects on salivary production or saliva chemistry

Science Question 2: Inhalation Cancer Dose-Response Modeling – Painesville Cohort Updated Mortality Study

Key Points

1. **It is recommended that the new Painesville study be included in updates of the evidence table for lung cancer from inhalation exposure to Cr(VI).**
2. **Positive exposure-response for lung cancer mortality is observed, providing new data for dose-response modeling and the cancer risk assessment for airborne Cr(VI).**

Mina Suh

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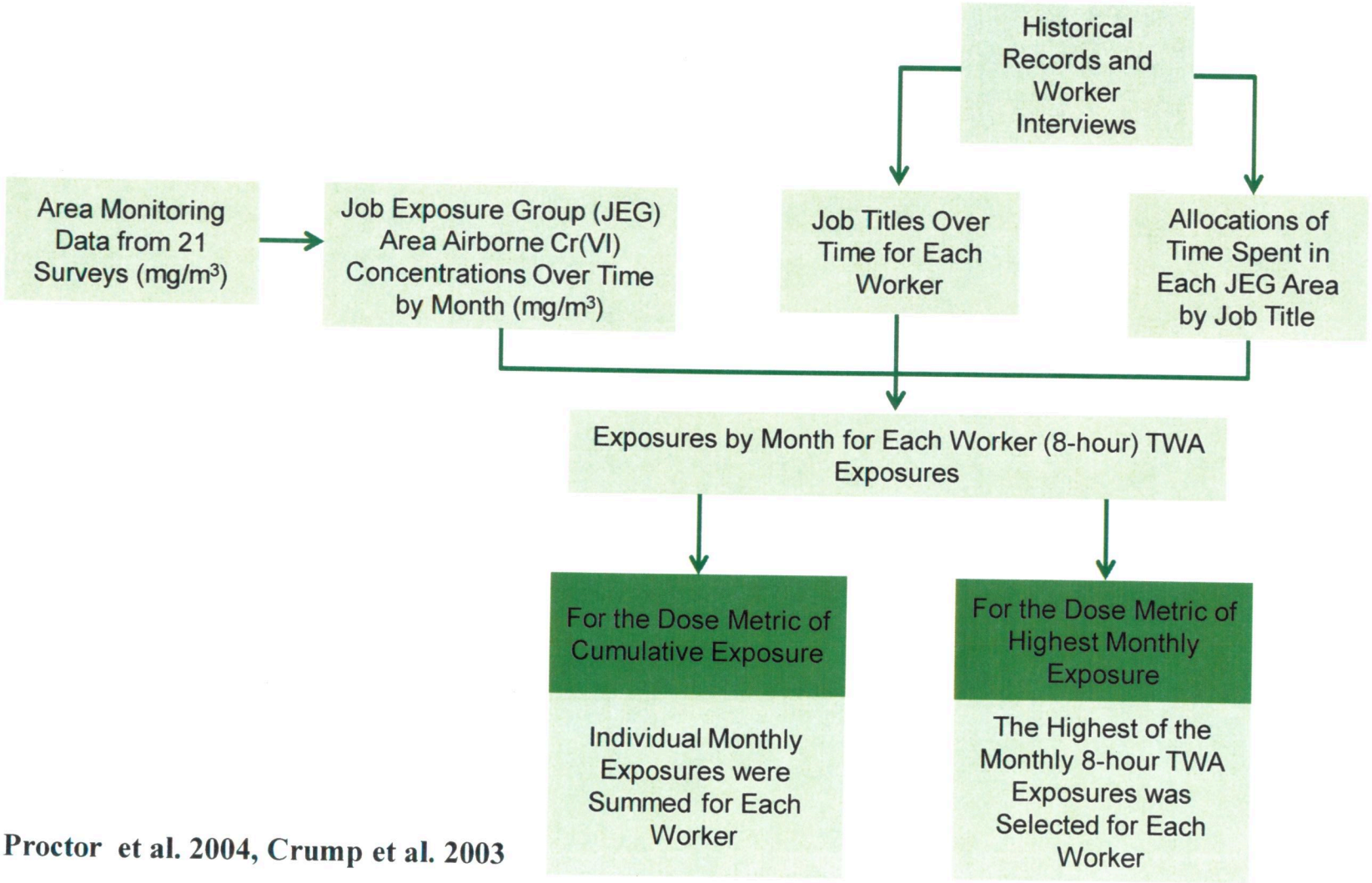
October 29, 2014

Background

- **The risk of lung cancer among chromate production workers has been used in several quantitative Cr(VI) risk assessments**
- **One of the most studied cohorts is from the Painesville Ohio facility, and previous follow-up was through 1997 (Luippold et al. 2003). Short-term workers were excluded in the previous study**
- **Funded by the Electric Power Research Institute (EPRI), updated study was conducted by researchers from ToxStrategies and SciMetrika**
- **Study objectives:**
  - Conduct updated mortality assessment (including 198 short-term workers) of chromate production workers in the Painesville facility
  - Conduct dose-response modeling to quantify lung cancer risk from environmental exposure
- **Manuscript is preparation and will be submitted in Q4 2014**

Exposure Reconstruction: Job Exposure Matrix Approach



Source: Proctor et al. 2004, Crump et al. 2003

Comparison of the Mortality Follow-Ups

Study Variable	Updated Study	Luippold et al. (2003)
Study population (N)	714	482
Follow-up period	January 1, 1940 to January 31, 2011	January 1, 1940 to December 31, 1997
Total person-years at risk	24,535	14,048
Deceased, n Alive LTF, n (%)	658 32 24 (3.4%)	303 136 43[a] (8.9%)
Deaths from cancer of the trachea/bronchus/lung, n	77	51
Cumulative exposure, mg/m^3-year	Mean: 1.10 Range: 0.0002 to 22.1	Mean: 1.58 Range: 0.003 to 23
Workers with ≤ 1.00 mg/m^3-year	518 (73%)	290 (60%)

a Forty-seven employees had unknown vital status at the end of study. Four did have substantial follow-up, just short of the end of the study period (Luippold et al. 2003)

Updated Mortality Assessment of the Painesville Cohort (Select Endpoints)

SMRs (95% CIs)	Updated Study	Luippold et al. (2003)
All Causes		
Observed (n)	658	303
Ohio	138 (127 to 148)	129 (115 to 144)
US	145 (127 to 148)	134 (120 to 150)
All Cancers		
Observed (n)	167	90
Ohio	146 (124 to 168)	155 (125 to 191)
US	155 (132 to 179)	166 (133 to 204)
Cancers of the trachea/bronchus/lung		
Observed (n)	77	51
Ohio	**186 (145 to 228)**	**241 (180 to 317)**
US	205 (159 to 250)	268 (200 to 352)

Characteristics of the Short-Term Workers (Updated Mortality Study)

Study Variable	Results
Population (N)	198
Deceased LTF	185 7 (**30% of LTFs)
Cumulative exposure, mg/m^3-year	Mean: 0.12 Range: 0.0002 to 0.69
All-cause SMR (95% CI)	
Observed (n)	185
Ohio	152 (130 to 174)
US	160 (137-183)
Lung cancer SMR (95% CIs)	
Observed (n)	14 (18% of LC deaths)
Ohio	134 (64 to 204)
US	147 (70-224)

- **Higher all-cause SMR compared to the entire cohort with lower cumulative exposure—Indicative of poor health status**
- **Consistent with what TCEQ noted in regards to short-term workers (Gibb et al. 2000, Baltimore cohort)**

Stratified Lung Cancer Mortality Risk by Cumulative Exposure (Updated Mortality Study)

Cumulative Exposure, mg/m^3-year	Workers (n)	Person-years	Lung Cancer Death Observed (n)	Lung Cancer SMR (95% CI)
0.000-0.031	70	1,832	4	111 (2 to 220)
0.032-0.066	72	2,448	7	179 (46 to 312)
0.067-0.136	76	2,408	4	112 (2 to 222)
0.137-0.204	67	2,370	2	44 (0 to 105)
0.205-0.331	72	2,420	5	119 (15 to 223)
0.332-0.547	73	2,707	9	182 (63 to 300)
0.548-0.831	69	2,390	3	68 (0 to 146)
0.832-1.569	72	2,634	14	355 (169 to 540)
1.570-3.235	71	2,503	8	189 (58 to 319)
3.236-22.112	72	2,823	21	533 (305 to 762)

- **Significant dose-response trend reported ($p<0.01$)**
- **Provides new data for dose-response modeling and cancer risk assessment for airborne Cr(VI)**
- **High degree of variability is observed with 10 exposure categories**